UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,592	07/21/2000	George Jackowski	3308.1001-000	5328

21005 7590 01/15/2003

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
COOK, LISA V	
ART UNIT	**PAPER NUMBER**
1641	23

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/621,592	JACKOWSKI, GEORGE	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-34 and 40-61* is/are pending in the application.

4a) Of the above claim(s) *40-43, 46-53 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *21,23-34,44,45,54-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *21,23-34 and 40-61* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicants' election with traverse of Group I (claims 21, 23,-34, 44-45, and 54-60) in Paper #22, filed 9/26/02 is acknowledged. Applicant does not traverse the Restriction Requirement on the grounds of lack of patentable distinctness. The traversal on the ground(s) "that the search required for each inventive group is similar and would not pose an undue burden on the Examiner". Specifically Applicant contends that the methods of Group I, II, and III are interrelated as genus and species and taken together would not place an undue burden upon the Examiner. This is not found persuasive because MPEP § 808.02 recites:

> Where related inventions as claimed are shown to be distinct under the criteria of MPEP § 806.05(c)- § 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof, (B) A separate status in the art when they are classified together, or (C) A different field of search.

In the instant case, (A) -The Restriction Requirement under 35 U.S.C. § 121 in Paper #20 established distinctness of the inventions:

A. Group I - claims 21, 23-34, 44-45, and 54-60 are drawn to a method for the differential diagnosis of ischemic and hemorrhagic cerebral events, determining at least *one* of the following brain injury, assessing NSE, endothelial cell membrane protein, MBP, and S100 comprising steps a-e, classified in class 435, subclass 7.92, for example.

B. Group II - claims 40, 42-45, and 61 are drawn to a method for determining that brain injury has occurred via *two or more* proteins selected from NSE, endothelial cell membrane protein, MBP, and S100 comprising steps a-c, classified in class 435, subclass 7.92, for example.

C. Group III - claims 41-53, are drawn to a methods for the diagnosis of ischemic and hemorrhagic cerebral events assessing *all* of the following four proteins NSE, endothelial cell membrane protein, MBP, and S100 comprising steps a-d, classified in class 435, subclass 7.92, for example.

With respect to the same reagents selected from the group consisting of it is noted that the methods of claim 21 in Group I and of claim 40 Group II requires the analysis of two markers however they differ because Group II measure brain injury. Brain injury is not fully encompassed within the method of Group I wherein ischemic and hemorrhagic cerebral events are measure. Group III is diverse from the other methods in that it requires the measurement of all four markers. The methods employ different reagents selected from the same Markush group. Although listed in the Markush format each individual protein is distinct and correlates to a different measurable events. Accordingly methods utilizing the reagents individually are patentably distinct.

(B) The inventions of Groups I -III would require a separate status in the art when they are classified together; the inventions are directed to diagnostic methods of blood analyses when taken as a whole would be classified in class 424 subclass 2 for example.

(C) With respect to a different field of search – Because these inventions are distinct and have acquired separate status in the art as shown by their different classification, recognized divergent subject matter and because the search required for each invention is not substantially coextensive with the search required for the remaining invention, restriction for examination purposes as indicated is proper.

Please note that the classifications in the restriction are illustrative only and do **not** represent all the classes and subclasses, which must be searched for each invention; nor is the search limited to issued US patents, but rather includes published foreign patents and applications as well as literature search.

2. For these reasons the inventions of Group I -III were not joined.

The Restriction Requirement is still deemed proper and is therefore made **FINAL.**

3. Currently, claims 40, 42-45, 61/Group II and claims 41-53/Group III are subject to Restriction and Election Requirement. The aforementioned claims have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as claims drawn to a non-elected invention. Claims 21, 23-34, 44-45, and 54-60 are under examination.

OBJECTIONS WITHDRAWN

Oath/Declaration

4. The new oath or declaration submitted 8/12/02 in paper #21 has obviated the objection to the Oath/Declaration. The objection is withdrawn.

OBJECTIONS MAINTAINED

Drawings

5. The formal drawings filed 3/30/01 in this application have been objected to by the Draftsperson under 37 CFR 1.84 or 1.152 (see PTO-948). Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

Claim Objections

7. Claim 34 remains objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 34 necessitates the analysis of all four markers via steps 1-6. However claim 21 merely requires the detection of brain endothelial cell membrane and one other marker.

Response to Argument

Claim 34 has been amended to clearly indicate the assessment of patient condition. However the claim still requires the measurement of all four marker in the assessment. See claim 34 line 1 "if MBP, S100, NSE and brain endothelial cell membrane proteins are assessed". While claim 21 merely requires the detection of brain endothelial cell membrane and one other marker.

NEW GROUNDS OF REJECTION NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 21, 23-34, 44-45, and 54-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 21 is vague and indefinite in reciting of method for the differential diagnosis of ischemic and hemorrhagic cerebral events. This is not clear because the claim only requires the measurement of two markers, one being a brain endothelial cell membrane protein and the other selected from the group consisting of MBP, S100, and NSE. However the measurement of only a brain endothelial cell membrane protein (like Tm) indicates an lunar infarct, while MBP indicates a intracerebral hemorrhage, NSE alone indicates TIA, and S100 alone indicates cerebral infarct. This was assessed in figure 2 of the disclosure. It is not clear how only two markers will measure differential ischemic and hemorrhagic cerebral events. For example if a brain endothelial cell membrane protein (like Tm) identifying a lunar infarct is measured along with only NSE which indicates TIA (transitory ischemic attack), how will these two proteins distinguish between ischemic and hemorrhage cerebral events. Appropriate correction is required.

B. Claims 26 and 27 are drawn to a method that requires a secondary marker which is "cell type specific of" the other markers utilized in the method. This claim is vague and indefinite because it is not clear as to what "cell type specific" applicant is referring. It is suggested that applicant include the specific cell type to obviate this rejection.

C. New claim 34 is vague and indefinite because it appears to detect NSE, MBP, and S100. However it is dependent on claim 21 which merely requires that one of these proteins be detected. Please clarify.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 21, 23-33, 44-45, and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method that differentially diagnosis between an ischemic cerebral event and a hemorrhagic cerebral events employing four specific markers (a brain endothelial cell membrane protein, MBP, S100, and NSE) it does not reasonably provide enablement for a method that measures only two of the markers. The assessment of all four markers is outlined in Figure 2.

The mere presence of any two does not provide information to distinguish ischemic and hemorrhagic cerebral events as recited in independent claim 21. For example if a brain endothelial cell membrane protein (like Tm) identifying a lunar infarct is measured along with only NSE which indicates TIA (transitory ischemic attack), how will these two proteins distinguish between ischemic and hemorrhage cerebral events. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation.

Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method for differential diagnosis of ischemic and hemorrhagic cerebral events employing two markers. However the analysis of only two markers does clearly distinguish these two events.

The state of the prior art- the prior art of record fails to disclose a method that is applicable to differential diagnosis of ischemic and hemorrhagic cerebral events. If one of the specific indicators is not clearly measuring an ischemic cerebral event while the other markers is directed to only a hemorrhagic event, the detection is not operable. How will the measurement of only a brain endothelial cell membrane protein (like Tm) which indicates an lunar infarct, along with MBP indicating an intracerebral hemorrhage, or NSE alone indicating TIA, or S100 alone indicating cerebral infarct measure differential ischemic and hemorrhagic cerebral events? This assessment requires the measurement of all four markers as exhibited in figure 2 of the disclosure.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed method is operable without a correlation between all four markers.

The amount of direction or guidance present- The specification fails to provide any guidance to enable the claimed method to function instances where only two of the markers are measured. Wherein the markers are specific to what is being assessed.

The presence or absence of working examples- no working examples are provided in the specification that show only two markers allowing for differential diagnosis as claimed. There are no working examples that show analogous results in an assay method that does not require a correlation between only two markers, which would be encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed. Neither the prior art nor the specification identifies methods to measure differential ischemic and hemorrhagic cerebral events utilizing one two markers from the group recited. Without such a correlation/relationship accurate detection cannot be determined.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method to measure differential ischemic and hemorrhagic cerebral events.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed method for the differentiation of cerebral events (ischemic and hemorrhagic) employing only two of the markers listed in claim 21, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work without a correlation to all four markers; 3) there is no proper guidance that shows how the markers are specific to an cerebral ischemic or cerebral hemorrhagic events which would render only two of the markers necessary for such a distinction, in the instant specification, 4) the nature of the invention is a method differentiates cerebral

ischemic or hemorrhagic events, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows such a distinction with the cited markers, and lastly 7) the claims broadly recite such a method, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Double Patenting

10. Double patenting obviousness-type rejection:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 21, 34, and 54-59 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of US patent 36,235,489.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to a method of analyzing the same four marker with respect to the distinction of a hemorrhagic cerebral event and an ischemic cerebral event.

This invention is encompassed within Patent # 6,235,489 wherein the same four markers are employed. In the Restriction Requirement in the parent application the analysis of all four markers was restricted from method detection only two of the markers.

Since the instant application is directed to "all four markers", it reads on the same inventive scope of patent #6,235,489.

12. For reasons aforementioned, no claims are allowed.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
Art Unit 1641
CM1-7B17
1/10/03

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
1/13/03